ORIGINAL ARTICLE

Exposure to non-arsenic pesticides is associated with lymphoma among farmers in Spain

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An appendix to this article is available on our website

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Objectives: To estimate the risk of lymphoma among farmers in Spain.
Methods: This is a multicentre case control study conducted in Spain. Cases were subjects diagnosed with lymphoma according to the World Health Organization (WHO) classification in four hospitals between 1998–2002. Hospital controls were frequency matched to the cases by sex, age, and centre. All subjects were interviewed about jobs ever held in lifetime for at least one year and the exposures in those jobs were recorded. The risk of lymphomas among subjects ever having had a job as a farmer was compared with all other occupations. Farmers were analysed according to the type of farming job performed: crop farming, animal farming, and general farming. Occupational exposure was summarised into 15 main categories: organic dust, radiation, contact with animals, PAH, non-arsenic pesticides (carbamates, organophosphates, chlorinated hydrocarbons, triazines and triazoles, phenoxy herbicides, chlorophenols, dibenzodioxin, and dibenzofuran), arsenic pesticides, contact with meat, contact with children, solvents, asbestos, soldering fumes, organic colourants, polychlorinated biphenyls, ethylene oxide, and hair dyes.
Results: Although farmers were not at an increased risk of lymphoma as compared with all other occupations, farmers exposed to non-arsenic pesticides were found to be at increased risk of lymphoma (OR = 1.8, 95% CI 1.1 to 2). This increased risk was observed among farmers working exclusively either as crop farmers or as animal farmers (OR = 2.8, 95% CI 1.3 to 5.8). Risk was highest for exposure to non-arsenic pesticides for over nine years (OR = 2.4, 95% CI 1.2 to 2.8).
Conclusions: Long term exposure to non-arsenic pesticides may induce lymphomagenesis among farmers.

In the past decades, the incidence of non-Hodgkin's lymphoma (NHL) has doubled in almost all westernised countries.[1,2] However, in the USA this increase has stagnated.[3] The causes in the increase of NHL are largely unexplained. A known predisposing factor that is strongly associated with NHL is immunosuppression.[1,2,4] A few other risk factors have been identified,[5,6] including exposure to infectious agents[1,2,7,8] and chemical and agricultural exposures.[1,2] Many of these exposures are occupational.[9] Attention has focused on farmers because they experience several of these exposures, including exposure to zoonosis, pesticides, and other chemicals such as fertilizers and solvents.[10,11] Farmers, and particularly those using pesticides, have been identified to be at an increased risk of lymphoid neoplasms.[10,12–15] However, these findings have not been confirmed by all studies.[4,11,13,16–18] Studies that investigated the genetic basis of lymphoma showed a relation between farming and lymphoma and pesticide exposure and lymphoma.[19,20] Many pesticides are carcinogenic in animals. They can act through several mechanisms to cause cancer in animals, but their role in human carcinogenesis remains partly unclear. Alteration of immune function is a known cause of human cancer and may be responsible for the carcinogenity associated with some pesticides.[21]

The objective of this study is to describe the risk of lymphoma among farmers with respect to type of farming job, type of exposures, and duration of exposures within the framework of the Spanish Epilymph case control study.

METHODS

A case control study was conducted in four hospitals in Spain within the framework of the European Epilymph study. The objective of the Epilymph project is to study infectious, occupational, and environmental risk factors on the aetiology of lymphoma.

Study population

Cases were subjects over 19 years old newly diagnosed with lymphoma between 1998 and 2002 in four centres in Spain (one in Barcelona, two in Tarragona, and one in Madrid). The diagnosis was verified by histology and 99% of them were supplemented by immunohistochemistry tests and flow cytometry. Cases were categorised according to the World Health Organization (WHO) classification for Neoplastic Diseases of the Lymphoid Tissues and included B cell, T cell, multiple myeloma, and Hodgkin's lymphoma. The International Classification of Diseases-O-3 codes included are 9650–55, 9659, 9663–67, 9667, 9670–71, 9673, 9678–80, 9684, 9687, 9689–91, 9695, 9698–02, 9705, 9708–09, 9714, 9716–19, 9728–29, 9731–32, 9734, 9761, 9823, 9826–27, 9831–37, 9940, and 9948.

Controls were hospital patients randomly chosen from among subjects admitted to different hospital wards and outpatient clinics within the hospital. A variety of diagnoses were included. Cancer patients (especially melanoma and skin cancer), patients with systemic infection, previous history of organ transplantation, or patients with severe systemic diseases were excluded. Controls were frequency matched by sex, age, and centre. No upper age limit was set for cases and controls, but all subjects had to be able to answer a structured and lengthy questionnaire. Ethical

Abbreviations: NHL, non-Hodgkin's lymphoma; PCB, polychlorinated biphenyl.

approval for the study was obtained from the local ethics committee. All subjects gave their written informed consent.

Data collection

All interviewers were trained specifically for the study. Cases and controls were interviewed in person and answered a lifestyle questionnaire which contained information on medical history and use of medication, residential changes, UV exposure, reproductive history, alcohol and tobacco habits, skin and hair colour, and use of hair dyes. Questions regarding occupational history were asked for each job ever held (for at least one year) since leaving school. Jobs were listed chronologically and described with respect to the activity of the company and the occupation and tasks of the subject. The interviewer listed a series of exposures of interest (for example, pesticides, solvents, dust, animals) for each job. For each of these exposures the subject specified if the exposure occurred during work, determined the kind of exposure, explained the reason for the exposure, and specified the years of exposure. After finishing the job history, the subject was asked about any extra jobs in crop farming or animal feeding. Later, this information was summarised into a list of 15 main exposures: organic dust, radiation, contact with animals, PAH, non-arsenic pesticides, arsenic pesticides, contact with meat, contact with children, solvents, asbestos, soldering fumes, hair dyes, organic colourants, ethylene oxide, and polychlorinated biphenyl (PCB). A specialised hygienist and an expert in occupational exposure assessment (both blind to the case control status of the subject) then produced an exposure assessment profile for a list of chemicals based on the questionnaire information. Of the 15 evaluated exposures, three were eventually left out of analysis (hair dyes, ethylene oxide, and PCBs) because very few people had been exposed to them. Non-arsenic pesticides included carbamates, organophosphates, chlorinated hydrocarbons (as pesticides), triazines and triazoles, phenoxy herbicides, chlorophenols, dibenzodioxin, and dibenzofuran. Grouping pesticides according to their chemical structure (arsenic *v* non-arsenic) is based on the assumption that substances with a similar chemical structure would exert their effects on humans in the same cells and through a similar mechanism of action.[22]

Jobs and exposures

All jobs were coded according to the Revised Edition 1968 of the International Standard Classification of Occupations.[23] Jobs were coded into five-digit codes for occupation and four-digit NACE (revision 1) for economic activity of the employer. Social class was deducted from three-digit ISCO codes of the last job held in the occupational history.[24] There were five social classes, with I as highest and V as lowest. For the current study, social classes II and III and social classes IV and V were grouped together. Participants that had never had a job, were retired, students, or housewives were coded as "unclassified".

Farmers were defined under the two ISCO codes 6-1 and 6-2. Subjects in group 6-1 were farmers involved in the production of a variety of agricultural and animal husbandry products. This group can be subdivided in general farmers (6–11) and specialised farmers (6–12). The group 6-2 consists of agricultural and animal husbandry workers. People in this group perform various tasks including growing field and market garden crops, cultivating trees, shrubs, and flowers, breeding and raising livestock and poultry, operating farm machinery, and related agricultural and animal husbandry work. They can be subdivided into general farm workers (6–21), field crop and vegetable farm workers (6–22), orchard, vineyard, and related tree and shrub crop workers (6–23), livestock workers (6–24), dairy farm workers (6–25), poultry farm workers (6–26), nursery workers and gardeners (6–27), farm machinery operators (6–28), and agricultural and animal husbandry workers not elsewhere classified (6–29). Each of these groups had several subcategories. When necessary, five-digit ISCO codes were used for analysis. Three-digit codes were used when five-digit codes did not add any relevant information.

For the current study, farmers were analysed according to the type of farming job performed: crop farming, animal farming, and general farming. These groups were compiled based on the tasks performed in the jobs. Subjects in each of the groups were people who had exclusively worked in that type of farming or who had worked most of the time of their farming jobs in that type of farming. An overview of which farming jobs were included in each group is included in the appendix (see http://www.occenvmed.com/supplemental).

Disease classification

According to the WHO classification, lymphoid neoplasms were grouped in B cell lymphoma (chronic lymphocytic leukaemia, lymphoplasmatic lymphoma, splenic marginal zone lymphoma, marginal zone B cell lymphoma, follicular lymphoma, diffuse large cell lymphoma, other B cell lymphoma), T cell lymphoma (mycosis fungoide/Sezary, other T cell), and Hodgkin's lymphoma. Multiple myeloma was reported separately in this study, but belongs in the classification of B cell lymphoma according to the WHO classification. The group of B cell lymphoma was thus analysed excluding multiple myeloma in this study.

Statistical analyses

Analyses were conducted for ever farming and for farming as longest occupation. Unconditional logistic regression was used to estimate the odds ratios and the 95% confidence intervals to measure association between working in farming and lymphoma risk. Several occupational groups were used in the data analyses. These were as follows: (a) farmers were compared to people who had never held a farming job; (b) pesticide exposed farmers were compared to non-exposed farmers; and (c) crop farmers, animal farmers, and general farmers were compared to subjects who had never held a

Table 1 Distribution of study subjects by gender, age, study centre, and social class

	Control	Case
	n (%)	n (%)
Total	628 (100)	587 (100)
Sex		
Male	325 (51.8)	329 (56.0)
Female	303 (48.2)	258 (44.0)
	p = 0.13	
Age (years)		
⩽46	165 (26.3)	137 (23.3)
47–63	163 (26.0)	143 (24.4)
64–72	151 (24.0)	155 (26.4)
⩾73	149 (23.7)	152 (25.9)
	p = 0.46	
Study centre		
Barcelona	526 (83.8)	464 (79.0)
Madrid	54 (8.6)	70 (11.9)
Tortosa	26 (4.1)	25 (4.3)
Reus	22 (3.5)	28 (4.8)
	p = 0.15	
Social class		
I	16 (2.5)	26 (4.4)
II–III	85 (13.5)	96 (16.4)
IV–V	348 (55.4)	329 (56.0)
Unclassified	179 (28.5)	136 (23.2)
	p = 0.04	

Table 2 Odds ratios and 95% confidence intervals for people who have ever been a farmer and people who had farming as longest occupation

	Controls/ cases	OR*	95% CI
Total lymphomas			
Never farmer	435/397	1	
Ever farmer	193/190	1.02	0.78–1.34
Farming as longest occupation	80/94	1.25	0.88–1.77
B cell lymphoma			
Never farmer	435/261	1	
Ever farmer	193/131	1.02	0.75–1.37
Farming as longest occupation	80/66	1.24	0.84–1.84
Multiple myeloma			
Never farmer	435/51	1	
Ever farmer	193/33	1.01	0.60–1.70
Farming as longest occupation	80/16	1.09	0.56–2.11
T cell lymphoma			
Never farmer	435/29	1	
Ever farmer	193/16	1.19	0.58–2.43
Farming as longest occupation	80/6	1.13	0.42–3.04
Hodgkin's lymphoma			
Never farmer	435/56	1	
Ever farmer	193/10	0.90	0.41–1.98
Farming as longest occupation	80/6	1.20	0.45–3.25

*Adjusted for age, sex, study centre, and social class.
Each of these groups was compared to the group of never farmers.

farming job. Standard statistical procedures were carried out using SPSS version 9.0. Chi-squared tests for differences between groups were used to compare cases and controls with respect to age, sex, study centre, and social class. Two-sided p values were considered statistically significant at the 0.05 level.

RESULTS

Of all eligible subjects, a total of 631 controls (96%) and 591 cases (82%) were included in the study. Seven (0.6%) subjects were later excluded because there was no information available on any of their occupations. The total number of analysed subjects was 628 controls and 587 cases. Of all subjects, 654 (53.8%) were male. The mean (standard deviation) age was 58.8 (17.3) years (58.0 (17.5) for controls and 59.8 (16.9) for cases, respectively). Table 1 shows the distribution of study subjects with respect to gender, age, study centre, and social class. No statistically significant differences were observed between cases and controls with respect to age, sex, or study centre. There was a statistically significant difference (p = 0.04) for social class due to the relatively large number of controls that was under unclassified categories (that is, retired, students, housewives) compared to cases.

Most of the lymphoma cases in our population were classified as B cell lymphoma (n = 392, 66.8%) with the most common subtype being chronic lymphocytic leukaemia (n = 125, 21.3%). There were 84 multiple myeloma cases (14.3%), 45 cases (7.7%) were diagnosed with T cell lymphoma, and 66 (11.2%) had Hodgkin's lymphoma. The distribution of the medical conditions of the controls included was: 14.7% surgical procedures, 14% ocular diseases, 15.6% diseases of the circulatory system, 12% injury and poisoning, 9.1% diseases of the respiratory system, 8.9% diseases of the urogenital system, 8.2% diseases of the gastrointestinal system, 4.1% diseases of the gynaecological system, 3.3% infections, 2.6% skin disorders, 2.4% diseases of the liver, 1.9% behavioural problems, 1.4% diseases of the endocrine system, 0.2% diseases of the haematological system, and 1.6% diseases of the cerebral system.

There were 383 subjects (31.5% of study population) who could be identified as ''ever farmer''. As compared to all other subjects, farmers were more likely to be male (66% *v* 48%, $p<0.01$), older (67.3 years *v* 55.0 years, $p<0.01$) and to be of a lower social class (68% *v* 50%, $p<0.01$) compared to all other subjects.

Of 383 identified farmers, 42 (11%) had missing years of duration for their farming jobs and were not included in the analysis of farming as longest occupation. However, they were included in the assessment of the overall risk for farmers and for the different types of farming.

There were 174 individuals who could be grouped as ''farming as longest occupation''. The mean (SD) duration of their farming job was 28.9 (17.5) years, with a minimum of two years and a maximum of 70 years.

Odds ratios with their 95% CIs for different lymphoma subtypes among farmers are shown in table 2. Results are summarised for farmers compared to never farmers and for farming as longest occupation compared to never farmers. ORs for subjects who have ever held a farming job are not significantly elevated. For individuals who had farming as longest occupation very moderate increases in risks were observed for ''all lymphoma'', B cell lymphoma, and Hodgkin's lymphoma (ORs 1.25, 1.24, and 1.20 respectively), but none of the estimates reached statistical significance.

One hundred and forty four (37.6%) farmers had worked exclusively or mostly in crop farming, 54 (14.1%) exclusively or mostly in animal farming, and 185 (48.3%) were categorised as general farming. Farmers categorised as crop farmers and animal farmers were not at any increased risk of any lymphoma as compared to never farmers. General farmers had a significantly increased risk of lymphoma (OR = 1.4, 95% CI 1.0 to 2.0) and a non-significant increased risk of B cell lymphoma (OR = 1.4, 95% CI 0.9 to 2.0) (table 3).

Among all farmers, 42% of them reported ever use of any pesticide. Most pesticide exposure was in general farming: 46.5% had ever used any pesticide. In crop farming, 36.8% ever used any type of pesticide and in animal farming this percentage was 40.7%. When lymphoma risk was evaluated for the different exposure categories stratified by group of

Table 3 Odds ratios and 95% confidence intervals for crop farmers, animal farmers, and general farmers as compared to never farmers

	Crop farmer			Animal farmer			General farmer		
	Controls/ cases	OR*	95% CI	Controls/ cases	OR*	95% CI	Controls/ cases	OR*	95% CI
Total lymphoma	83/61	0.7	0.5–1.1	31/23	0.8	0.4–1.3	79/106	1.4	1.0–2.0
B cell lymphoma	83/41	0.7	0.4–1.1	31/18	0.9	0.5–1.6	79/72	1.4	0.9–2.0
Multiple myeloma	83/10	0.7	0.3–1.5	31/4	0.9	0.3–2.8	79/19	1.2	0.7–2.3
T cell lymphoma	83/6	1.1	0.4–2.9	31/1	0.5	0.1–3.5	79/9	1.5	0.6–3.7
Hodgkin's lymphoma	83/4	0.7	0.2–2.2	31/–	NA†	NA†	79/6	1.6	0.6–4.3

*Adjusted for age, sex, study centre, and social class.
†Not applicable due to empty cells.

Table 4 Risk of lymphoma by occupational exposure categories among crop and animal farmers and general farmers

	Farmers				Crop and animal farmers				General farmers			
	Controls (%)	Cases (%)	OR*	95% CI	Controls (%)	Cases (%)	OR*	95% CI	Controls (%)	Cases (%)	OR*	95% CI
Organic dust	192 (99.5)	186 (97.9)	0.2	0–1.9	113 (99.1)	82 (97.6)	0.2	0–2.6	79 (100)	104 (98.1)	NA	NA
Radiation	185 (95.9)	182 (95.8)	1.1	0.4–3.2	110 (96.5)	78 (92.9)	0.4	0.1–1.7	75 (94.9)	104 (98.1)	3.8	0.6–22.8
Contact with animals	118 (61.1)	113 (59.5)	1.3	0.8–2.0	62 (54.4)	39 (46.4)	1.1	0.5–2.1	56 (70.9)	74 (69.8)	1.4	0.7–2.8
PAH	68 (35.2)	55 (28.9)	0.8	0.5–1.3	37 (32.5)	25 (29.8)	0.9	0.5–1.8	31 (39.2)	30 (28.3)	0.7	0.4–1.4
Non-arsenical pesticides	52 (26.9)	63 (33.2)	1.8	1.1–2.9	26 (22.8)	26 (31)	2.8	1.3–5.8	26 (32.9)	37 (34.9)	1.3	0.7–2.5
Solvents	56 (29)	46 (24.2)	0.8	0.5–1.4	24 (21.1)	18 (21.4)	1	0.5–2.3	32 (40.5)	28 (26.4)	0.6	0.3–1.1
Arsenical pesticidas	39 (20.2)	38 (20)	1.1	0.7–1.9	23 (20.2)	16 (19)	1.3	0.6–2.7	16 (20.3)	22 (20.8)	1.2	0.6–2.4
Contact with meta	59 (30.6)	50 (26.3)	0.9	0.6–1.5	20 (17.5)	16 (19)	1.5	0.7–3.1	39 (49.4)	34 (32.1)	0.5	0.3–1.0
Asbestos	41 (21.2)	39 (20.5)	1.2	0.7–2.0	19 (16.7)	10 (11.9)	0.9	0.4–2.1	22 (27.8)	29 (27.4)	1.2	0.6–2.3
Soldering fumes	23 (11.9)	26 (13.7)	1.4	0.7–2.7	12 (10.5)	7 (8.3)	0.9	0.3–2.7	11 (13.9)	19 (17.9)	1.6	0.7–3.9
Organic colourants	26 (13.5)	16 (8.4)	0.6	0.3–1.2	10 (8.8)	5 (6)	0.5	0.1–1.7	16 (20.3)	11 (10.4)	0.5	0.2–1.2
Contact with children	16 (8.3)	5 (2.6)	0.3	0.1–0.8	10 (8.8)	1 (1.2)	0.1	0–1	6 (7.6)	4 (3.8)	0.4	0.1–1.5

*Adjusted for age, sex, study centre, and social class.

farming, non-arsenic pesticides was the only exposure category significantly associated to lymphoma risk among farmers other than general (that is, crop and animal farming, OR = 1.8, 95% CI 1.1 to 2.9). Within the group of general farmers no association was found for any of the 12 exposure categories (table 4).

The mean (SD) duration of exposure to non-arsenic pesticides was 16.3 (13.0) years. 115 (30%) farmers were exposed to non-arsenic pesticides during their working period as such. For 111 of them, the number of years of exposure could be established. An increased risk was observed for all farmers and crop and animal farmers exposed to non arsenic pesticides for 9–17 years although no statistical significant trend was observed with further years of exposure (table 5).

DISCUSSION

In the data presented, people who had ever been a farmer had no increased risk of lymphoma compared to all other occupations. This was consistent with findings of some,[10 16 17] but not all studies.[10 12 22 25–27] Subjects who had farming as their longest occupation had a somewhat increased, but not significant, risk of all lymphomas together and specifically for B cell and Hodgkin's lymphoma. However, an increased risk of lymphoma was observed among farmers who had been exposed to non-arsenic pesticides as compared to non-exposed farmers. No increment in risk was observed among farmers for the 11 other predefined occupational exposures.

Grouping pesticides according to their chemical structure (arsenical *v* non-arsenical) is based on the assumption that substances with a similar chemical structure would exert their effects on humans in the same cells and through a similar mechanism of action.[22] However, many studies have classified pesticides according to their purpose (insecticides, herbicides, or fungicides) or the target pest,[12] which makes comparison across studies difficult. Many individual pesticides that were classified as non-arsenic pesticides in our data were found to be associated with increased lymphoma risk. Chlorophenols,[14 21 22] organochlorine insecticides,[13 21 22] organophosphate insecticides,[13 21 22] phenoxyacetic acid herbicides, DDT,[4 11] and carbamates were found to be associated with lymphoma.[14] In the study presented here, brand names and detailed years of use at work were requested. However, a number of subjects were unspecific in their answers and many of them knew they had been in contact with pesticides but could not recall the brand of the specific product. The expert coders used the available information together with the tasks performed at work to code the chemical exposure under specific categories. Therefore many subjects have been classified as being exposed to non-arsenic pesticides but more specific information is unavailable.

Further analysis of non-arsenic pesticides showed that farmers who had been exposed for long periods had an increased risk of lymphoma. This is consistent with findings from another study restricted to women who lived and worked on a farm where pesticides were used for more than 10 years.[12]

Although environmental exposure in Spain to pesticides has been reported to be among the highest in Europe[28] in our study 42% of the farmers reported ever use of pesticides. Few data are available in Spain about specific exposure to pesticides. A source of information about occupational exposure in Spain, the exposure information system CAREX indicates that agriculture accounts for 40% of all workers and that main exposure in the agriculture industry is solar radiation. Specific pesticides like polychlorinated biphenyls were not very common but no detailed information on specific pesticides is available in CAREX.[29]

Our definition of a farmer also included farm owners and farm managers. It is possible that these people do not apply pesticides themselves and are therefore not exposed.

Table 5 Odds ratios and 95% confidence intervals for farmers exposed to non arsenic pesticides as compared to non-exposed farmers

	All farmers			Crop and animal farmers			General farmers		
Length of use	Controls/cases	OR*	95% CI	Controls/cases	OR*	95% CI	Controls/cases	OR*	95% CI
Not exposed farmer	141/127	1		88/58	1		53/69	1	
Ever exposed farmer	52/63	1.8	1.1–2.9	26/26	2.8	1.3–5.8	26/37	1.3	0.7–2.5
1–8 years	18/16	1.5	0.7–3.2	11/9	2.4	0.8–7.2	7/7	1	0.3–3.1
9–17 years	16/25	2.4	1.2–4.8	7/10	4.2	1.4–12.6	9/15	1.5	0.6–3.9
18–60 years	16/20	1.7	0.8–3.5	7/7	2.4	0.8–7.7	9/13	1.2	0.5–3.1
Analysis for trend	p = 0.80			p = 0.58			p = 0.99		

Adjusted for age, sex, study centre, and social class.

However, only 63 of 383 farmers reported having ever worked as a farm manager (data not shown).

No associations were found for crop farming, animal farming, or general farming. Risks for crop farming and animal farming were actually slightly, but not significantly, decreased. We observed a moderate increased risk of lymphoma among subjects classified as general farmers. According to ISCO, general farmers work at or manage mixed farms. At these farms, a variety of agricultural and animal husbandry products is produced. The type of activity of general farmers cannot be clearly established and it is likely that exposures differ across individuals because of the wide variety of products produced and tasks performed. The exposures might also have changed over time, especially regarding chemicals used. This is the first time to our knowledge that different occupational groups of farming have been analysed with respect to their lymphoma risk.

Subsequent analysis by exposure category among general farmers and crop animal farmers identified an increased risk among crop and animal farmers associated with non-arsenical pesticides. This was the only association that reached statistical significance. Among general farmers the association with non-arsenical pesticides was not observed.

In this study the risks of ISCO classified farmers were evaluated, but in many studies it is not clear what is regarded as a farmer. Blair *et al*[16] state that the only information that was available in their meta-analysis was that on the broad category of farmer. For most other studies it is not clear whether a classification system was used to define farmers,[10] or subjects were simply asked if they had ever lived or worked on a farm.[12] These problems make the occupation ''farmer'' difficult to compare between studies.

Some studies do not investigate the occupation ''farmer'', but the exposure to pesticides, without explaining chemical class or purpose. Pesticides are mostly used by farmers, but other people (in packaging and/or manufacturing as well as in the general population) can also be exposed,[2 21 22] which makes comparison between farming studies and exposure studies difficult. Moreover, farmers experience multiple exposures.[4 10–15 21 22 25 30]

Another problem in comparing the current study to others is that the disease investigated differs between studies and/or that a different classification system may be used.[1 5 6] Classification systems differ according to the types of lymphomas included.

We analysed all lymphoma together as well as B cell, T cell, and Hodgkin's lymphoma separately. Most studies that investigate the cancer risk among farmers only evaluate the risk of NHL and not for subtype.[1 4 10 11 13 15 18 22 30] Kato *et al*[12] evaluated subtypes of NHL with use of pesticides. They found increased risks for different levels of exposure among women exposed to pesticides for both B cell and T cell lymphoma and for high grade lymphoma. Our data identified a moderate, non-significant, increased risk of T cell lymphoma.

Radiation in the current study consists of various types of radiation, from radioactive sources, radon, *x* rays, solar radiation, and artificial UV radiation. It is likely that most of the radiation was solar radiation, especially in the farming environment. A protective effect for NHL of solar radiation has been reported;[31–33] however, this is not confirmed by all studies. Moreover, the risks for NHL were found to be increased after diagnosis of skin cancer and the risks for skin cancer were increased after diagnosis of NHL. The investigators conclude that the increase in UV light exposure may have contributed to the increase in NHL,[34] but this has been criticised because the pathogenesis of skin neoplasms may be multifactorial[35] and the risk of NHL after skin cancer should be of the same magnitude as the risk of skin cancer after NHL.[36] Evidence remains inconclusive, but if UV light exposure really protects against NHL, this may have diluted our results because almost all farmers have been exposed to sunlight (and more farmers were exposed than people in other occupations). We found that farmers had no increased risk of lymphoma. However, we found increased risks for general farmers when occupational subgroups of farmers were analysed, although the risk was not statistically significant. If UV light exposure really is a confounder, then this should also have effects on these subgroups. It is reasonable to assume that all farmers spend a similar amount of hours working outdoors.

As in all retrospective case control studies, the exposure to agents could not be measured directly and information for this study was based on lifetime recall from personal interviews. Although recall bias can never be excluded, the wide extension of our questionnaire eliminating any specific attention on pesticides, the inclusion of hospital controls, and the specific association identified with non-arsenical pesticides but not with other exposures are reasons to believe that our results are unlikely to be explained by recall bias. Further, included patients as well as the interviewers were unaware of our study hypothesis. The expert hygienists were unaware of the disease status of the subject when estimating the probability of exposure.

In some cases it was difficult to estimate the duration of exposures within farming jobs, as use of chemicals did not always occur during the whole period of the job. For duration of the exposure, the year of the first occurrence of the exposure was used as the starting year, which did not always coincide with the start of the job. Sometimes information on years of exposure was missing but this was only the case for a small proportion of subjects.

In the current study the level or concentration, frequency, and probability of exposure were not evaluated. This would provide important information on the real exposure that people experienced. This information was partly available in the database, but not used in the current analysis.

The study has a comprehensive epidemiological design with many cases and controls from different hospitals. The inclusion rate of both cases and controls was high. Diagnosis of cases was reliable and these were also reviewed by an international panel of pathologists with a high level of confirmation.

The expert hygienist who evaluated the information on exposures was blind to the case control status of subjects, so this has not biased the classification of exposures.

Further research on farmers should be focused on identifying exposures among different types of farmers and relating these to their demonstrated increased risk. Also, information about when exposures took place is important, because the composition of chemicals used in pesticides changes and exposures may differ in time. The intensity, frequency, and probability of exposures should also be taken into account.

CONCLUSIONS

Farmers exposed to non-arsenic pesticides were found to be at an increased risk of lymphomas. The risk was clearly observed for crop and animal farmers. This risk was greatest when exposure to non-arsenic pesticides was for a period of 9–17 years. There is a need to monitor this association closely to take into account the potential hazardous effect of pesticides and to account for temporal variations in the chemical composition of pesticides.

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